-- At about 73 days of age, homozygous, heterozygous, and wild-type mice were analyzed for fasting whole blood glucose, serum insulin, and serum glucagon measurements. As shown in Figure 4, fasting blood glucose was greatly decreased in homozygous mutant mice, while heterozygous mutant mice had increased fasting blood glucose levels. The relationship between blood glucose levels and the severity of pancreatic lesions is demonstrated in Figure 5. Serum insulin levels were decreased in homozygous mutant mice, as shown in Figure 6, and the relationship of insulin levels to the severity of pancreatic lesions is shown in Figure 7. Glucagon levels were greatly elevated in homozygous mutant mice (see Figure 8) and these levels also correlated with the severity of the pancreatic lesions. --

REMARKS

I. Amendments

A. Claims

Claims 5-10 and 18-34 have been canceled. Claims 57-71 have been added. The newly added claims do not add or constitute new matter, and are completely supported by the application as originally filed. Support may be found throughout the specification and in the originally filed claims. Specifically, support for claim 57 may be found, for example, at page 55, line 17 through page 63, line 28, of the specification. Support for claims 58-65 can be found, for example, at page 58, line 7 through page 59, line 8 and at page 61, line 5 through page 63, line 28, of the specification. Support for claims 66-68 can be found, for example, at page 56, line 16 through page 57, line 5, of the specification. Support for claim 69-71 can be found, for example, at page 23, lines 24-31 through page 24, lines 1-8.

The amendments to the claims are made without prejudice to the pending or now canceled claims or to any subject matter pursued in related applications. Moreover, the amendments are made solely to expedite prosecution of the application and are not intended to limit the scope of the invention. The Applicants reserve the right to prosecute any canceled subject matter at a later time or in a later filed divisional, continuation or continuation-in-part application.

B. Specification

The amendment to the specification is made in order to correct a spelling error, and does not add or constitute new matter. Attached herewith is Appendix A, which includes a marked-up version of the amendment.

Upon entry of the amendments, claims 57-71 are pending in the instant application.

II. Sequence Compliance

The Examiner has noted that the instant application allegedly fails to comply with the requirements of 37 CFR 1.821 through 1.825, in particular because the sequence disclosed in Figure 2A lacks a sequence identifier. However, Applicants respectfully point out that in a preliminary amendment dated July 16, 2002, which was filed in response to a previous Notice To Comply dated June 19, 2002, Applicants filed a replacement Figure 2A which assigned a sequence identifier to the sequence disclosed in Figure 2A. As this sequence was already included in the submitted Sequence Listing (SEQ ID NO:1), Applicants believe that no substitute Sequence Listing is required, and that Applicants are in full compliance with the requirements of 37 CFR 1.821 through 1.825.

III. Objections

The Examiner has objected to the specification because the phenotype of the heterozygous mice in regards to glucose levels is allegedly contradictory as stated. In particular, the Examiner objects to the statement on page 62, lines 28-30, disclosing that the heterozygous mutant mice display decreased fasting glucose levels, in light of the statement on page 59, line 12, disclosing that the heterozygous mutant mice have increased fasting levels. The Examiner has interpreted the phenotype of the heterozygous mutant mice to be increased glucose levels, and has relied on Figure 4, which allegedly supports this phenotype.

Applicants submit that Figure 4 describes whole blood fasting glucose levels for the transgenic mice and wild-type control mice. The glucose measurements illustrated in Table 2 at page 59 of the specification shows that the heterozygous mutant mice (-/+), both male and female, exhibit reduced serum non-fasting glucose levels, relative to the wild-type mice (+/+). Further, Figure 9, which shows the results of a glucose tolerance test described beginning at page 61, line 16 (Example 4), supports the reduced glucose level phenotype of the heterozygous mutant mice, because the heterozygous mutant mice exhibit a statistically significant reduction in fasting glucose levels, relative to the wild-type control mice. Therefore, Applicants submit that

the specification discloses a phenotype of reduced fasting glucose levels for the heterozygous mutant mice.

IV. Rejections

A. Rejections under 35 U.S.C. § 112, first paragraph

Claims 5-10 and 18-34 were rejected under 35 U.S.C. § 112, first paragraph, because, according to the Examiner, the specification does not enable any person skilled in the art to which it pertains to make and use the invention commensurate in scope with the claims. Applicants respectfully traverse this rejection. However, in view of the cancellation of claims 5-10 and 18-34, the Examiner's rejection under 35 U.S.C. § 112, first paragraph, is no longer relevant.

Specifically, in the rejection, the Examiner asserts that due to the breadth of the claims and the knowledge and level of expertise in the art at the time of filing of the instant application, the specification allegedly does not provide an enabling disclosure for the transgenic animals and/or knockout mice or cells as recited in claims 5-10 and 18-34. More particularly, according to the Examiner, in light of the state of the art of ES cell technology, the specification does not provide adequate guidance for one of skill in the art to generate a non-human transgenic animal having a disruption in the glucagon receptor gene in any species other than a mouse. In addition, the Examiner asserts that, due to the unpredictability of the phenotype of a transgenic animal, the specification is not enabling for a transgenic animal, and specifically a mouse, which exhibits a phenotype other than that disclosed in the application. Further, the Examiner asserts that the specification is not enabling for the heterozygous mutant mice as claimed, in that the specification allegedly fails to disclose that the heterozygous mutant mice exhibit the phenotypes disclosed. Finally, according to the Examiner, the specification fails to provide an enabling disclosure for the preparation of a transgenic animal of either gender with a glucagon receptor disruption that exhibits infertility as encompassed by the claims.

The Applicants respectfully disagree with the Examiner's conclusions. However, claims 5-10 and 18-34 have been cancelled. Applicants submit that the specification provides sufficient enabling disclosure for the transgenic mice and cells as currently recited in new claims 57-71. More particularly, the scope of the current claims, which encompass transgenic mice whose genomes comprise a disruption in the endogenous glucagon receptor gene, which disruption, when homozygous, leads to a specific phenotype of a metabolic abnormality or a pancreatic abnormality,

or, in the case of homozygously disrupted pairs of mice, reduced fertility, is sufficiently enabled by the instant specification.

As this rejection under 35 U.S.C. § 112, first paragraph, of claims 5-10 and 18-34 is no longer relevant as a result of the cancellation of these claims, and new claims 57-71 are fully enabled by the teachings of the specification as noted above, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

B. Rejection under 35 U.S.C. § 112, second paragraph

Claim 26 was rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. Applicants respectfully traverse the rejection under 35 U.S.C. § 112, second paragraph. However, in light of the cancellation of claim 26, the rejection is no longer relevant.

C. Rejections under 35 U.S.C. § 103

Claims 5-10 and 18 were rejected under 35 U.S.C. § 103 (a) as being unpatentable over Capecchi, 1994, *Scientific American,* 270: 34-41 ("Capecchi") in view of Burcelin *et al.,* 1995, *Gene*, 164: 305-310 ("Burcelin") and further in view of Chambers *et al.,* 1996, *Nature Genetics,* 12: pp122 ("Chambers"). Applicants respectfully traverse this rejection. However, in view of the cancellation of claims 5-10 and 18, the rejection under 35 U.S.C. § 103 is no longer relevant.

Applicants submit that new claims 57-71 are non-obvious over the teachings of the prior art references. More particularly, the claimed invention relates to the *in vivo* mammalian characterization of the function of the glucagon receptor gene, and provides transgenic mice and cells comprising a disruption in the endogenous glucagon receptor gene, all of which are not obvious in view of the sole or combined teachings and disclosures of the references cited by the Examiner.

According to the Examiner, Capecchi discloses transforming a cell with a nucleic acid construct comprising a disruption in the *Hox*A-3 gene, resulting in an inactivating insertion of a selective marker gene into the endogenous *Hox*A-3 locus, and using said cell to generate a mouse whose genome comprises a disruption in the *Hox*A-3 gene. Capecchi very generally discusses the method of targeted gene replacement, specifically as it relates to disrupting the *Hox*A-3 gene. Capecchi then further specifically discusses the effect or phenotype of a knockout of the *Hox*A-3 gene in mice observed in his laboratory, which revealed a role for *Hox*A-3 in development of the mouse embryo.

Burcelin, as characterized by the Examiner, teaches the cloning and characterization of the mouse glucagon receptor gene, and provides the nucleic acid sequence for the glucagon receptor gene.

The Examiner relies on the teachings of Chambers to provide motivation to disrupt the glucagon receptor gene to determine its role in hypertension and diabetes. Specifically, Chambers describes a missense mutation in the glucagon receptor noted in human patients with late onset non-insulin-dependent diabetes mellitus (NIDDM). Chambers further describes the relation of this mutation to essential hypertension as well as insulin-dependent diabetes mellitus (IDDM).

In order to establish a *prima facie* case of obviousness, the Examiner must meet three basic criteria: there must be some suggestion or motivation to modify a primary reference or combine reference teachings; there must be a reasonable expectation of success; and the prior art reference(s) must teach or suggest all the claim limitations. See MPEP §2143.

The Examiner asserts that the ordinary artisan would have been motivated to combine the teachings of the prior art references to determine the role of the glucagon receptor in hypertension and diabetes, as mutations in the human glucagon receptor had been associated with these diseases as disclosed in Chambers. The Applicants respectfully disagree. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. See MPEP 2143.01. The Applicants submit that Chambers does not suggest the desirability of disrupting the glucagon receptor in a mouse. Therefore, the Examiner has failed to provide sufficient evidence in Chambers of the motivation or suggestion to combine the prior art references required to establish a case of *prima facie* obviousness.

Further, Applicants submit that the Examiner has failed to show that one of ordinary skill in the art would have a reasonable expectation of success to make a glucagon receptor knockout mouse based on the combined disclosures of the prior art references, and in particular, based on the disclosure of Capecchi, who discloses a very general method of targeted gene replacement, and Burcelin, who provides the sequence information and characterization for the glucagon receptor. Capecchi does not teach, suggest or contain any disclosure regarding GPCRs, let alone the glucagon receptor. That Burcelin merely provides the sequence of the glucagon receptor does not cure that failing. In any case, the Applicants have cancelled claims 5-10 and 18, and

submit that one of ordinary skill in the art would not have a reasonable expectation of success in combining the cited references to create the invention as recited in new claims 57-71.

Finally, in order to establish a *prima facie* case of obviousness, the Examiner must also show that the prior art references teach or suggest all of the claimed limitations. As described above, the disclosure of Capecchi is limited to generally discussing a method for producing targeted gene disruptions in a mouse, and specifically to the production of a *Hox*A-3 gene disrupted mouse. Burcelin is limited to providing disclosure related to the cloning and characterization of the glucagon receptor. The disclosure of Chambers merely discusses a missense mutation occurring in a small subset of NIDDM patients, and the potential role of the mutation or disease in essential hypertension.

However, neither Capecchi, Burcelin nor Chambers, alone or in combination, teaches all of the limitations as presently claimed. As acknowledged by the Examiner, Capecchi provides no disclosure or teaching of how to make a glucagon receptor gene knockout mouse. More particularly, Capecchi does not disclose a transgenic mouse comprising a disruption in a glucagon receptor gene, wherein the transgenic mouse exhibits a specific phenotype, particularly a phenotype of a metabolic abnormality or pancreatic abnormality, as claimed by the present invention. Likewise, Burcelin does not provide any teaching or suggestion relating to targeted disruptions in any gene, particularly in a glucagon receptor gene. More particularly, the disclosure of Burcelin fails to provide any teaching or suggestion that relates to transgenic mice or cells, and in particular to those transgenic mice and cells as recited in the pending claims. Further, Chambers fails to provide any teaching or suggestion of targeted disruption of the glucagon receptor gene in a mouse or cell, or to compositions related thereto as is currently claimed by the instant invention.

Taken together, the disclosures of Capecchi, Burcelin and Chambers are devoid of any teaching or suggestion of disrupting the glucagon receptor gene, and in particular, are deficient of any teachings or suggestions of the transgenic mice and cells as recited in the pending claims. More particularly, the disclosures of Capecchi, Burcelin and Chambers, alone or combined, do not teach or suggest in any way transgenic mice comprising disrupted glucagon receptor genes, wherein such transgenic mice exhibit a phenotype, and in particular exhibit a phenotype of a metabolic abnormality, pancreatic abnormality, a growth abnormality and wherein the mice are

mated, a fertility abnormality, or tissues and cells comprising the disrupted glucagon receptor gene as claimed by the present invention.

As the obviousness rejection is no longer relevant as result of the cancellation of claims 5-10 and 18, and new claims 57-71 are not obvious in view of the teachings of Capecchi, Burcelin and Chambers, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 103.

It is believed that the claims are in condition for allowance, and notice to that effect is respectfully requested. The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-1271 under Order No. R-648.

Respectfully submitted,

Date: April 7, 2003

Nicole A. Verona

Nicole A. Verona Reg. No. 47,153

Deltagen, Inc.
700 Bay Road
Redwood City, CA 94063
Tel. (650) 569-5100
Fax (650) 569-5280

Enclosure

Appendix A

(Version with markings to show changes made)

Paragraph beginning at page 59, line 9 of the specification:

At about 73 days of age, homozygous, heterozygous, and wild-type mice were analyzed for fasting whole blood glucose, serum insulin, and serum glucagon measurements. As shown in Figure 4, fasting blood glucose was greatly decreased in homozygous mutant mice, while heterozygous mutant mice had increased fasting blood glucose levels. The relationship between blood glucose levels and the severity of pancreatic lesions is demonstrated in Figure 5. Serum insulin levels were decreased in homozygous mutant mice, as shown in Figure 6, and the relationship of insulin levels to the severity of pancreatic lesions is shown in Figure 7. Glucagon levels were greatly elevated in homozygous mutant mice (see Figure 8) and these levels also correlated with the severity of the pancreatic lesions.